



JBP 246

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APR 21 1987

Applicant : Charles E. Clum et al. GROUP 120
Serial No. : 700,165 Art Unit: 125
Filed : February 11, 1985 Examiner: L. Schenkman
For : Skin Care Compositions

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87-2039

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

APPELLANTS' REPLY BRIEF ON APPEAL

Dear Sir:

This is a Reply Brief to the new points of argument raised in the Examiner's Answer dated March 2, 1987. The Examiner stated that "A declaration of Isaacson, filed April 8, 1986 was persuasive in substantiating synergism of a 1:60 mixture of miconazole nitrate and zinc oxide against one organism; Straphylcoccus aureus (sic). A second declaration of Semple, filed September 4, 1986, presented data regarding a 1:60 mixture of miconazole nitrate and zinc oxide vs. Casndida Albicans (sic). It is the Examiner's position that the shown enhancement of microbial inhibition $\approx 8-25\%$ is considered minimal and not seen to be a degree which definitively reflects synergism....".

It is respectfully contended that the Examiner's allegation that the showing in the Semple declaration of "enhancement of microbial inhibition...is considered minimal..." is incorrect. The Semple declaration of September 4, 1986 as well as the earlier Semple declaration of April 8, 1986 and the Leyden declaration of April 8, 1986 clearly demonstrate synergism of a 1:60 mixture of miconazole nitrate and zinc oxide against *Candida albicans*.


The declarations set forth a specific well-recognized in vivo test procedure and resulted in two different types of measurements and data being obtained; i.e. microbiological and clinical. The microbiologic results (the only results referred to by the Examiner) demonstrate a statistically significant synergistic effect. The test for synergism is not some absolute magnitude (apparently the position of the Examiner) but rather whether the results are statistically significant and such is the case here. As discussed on pages 9 and 10 of Appellants' Brief on Appeal and on pages 3 and 4 of the Semple declaration of September 4, 1986, this synergistic effect cannot be attributed to experimental error because of the precision of the experiment itself and particularly, the microbiological counts. The probability of an experimental error producing this synergistic effect is very small, i.e., $P < 0.05$. It is important to realize that the standard for this type of test procedure and evaluation of the data resulting from same is not one of absolute magnitude but rather one which establishes that the resultant effects cannot reasonably be attributed to random fluctuations or error. Such is clearly the case here thereby establishing statistical synergism. It should also, importantly, be noted that this is

a different test procedure than the in vitro procedure leading to the results in Table III of the specification, referred to by the Examiner in his Answer.

It is also important to note that the Examiner apparently has not considered the clinical measurements resulting from this in vivo test procedure on human skin. These are discussed and reported in the Semple declaration and the Leyden declaration. Furthermore, in the Semple declaration of September 4, 1986, these results are set forth graphically on page 5 of said declaration and clearly demonstrate the synergistic effects of a 1:60 mixture of miconazole nitrate and zinc oxide against *Candida albicans*. (See also pages 10 and 11 of Appellants' Brief on Appeal.)

Applicants respectfully contend that the above clearly establishes synergism for a 1:60 mixture of miconazole nitrate and zinc oxide against *Candida albicans* and together with the acknowledgement by the Examiner of the synergism of the same mixture against *Staphylococcus aureus*, demonstrates the allowability of the claims on appeal.

Respectfully submitted,


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